change between the data from the untreated animals and the data from the matched treated animals.

In the Claims:

Please cancel claim 2, and note that claims 14-19 have been previously cancelled.

Please amend claims 1, 3 and 4 as follows:

1. (Amended) A method for treating chronic neuroinflammation in a patient with neuroinflammatory autoimmune disease comprising administering to the patient an amount of Bowman Birk Inhibitor effective to reduce, inhibit, or suppress the chronic inflammation.
3. (Amended) The method of claim 1, wherein the neuroinflammation affects the central nervous system or peripheral nervous system of the patient.
4. (Amended) The method of claim 3, wherein demyelination of the neural tissue of the patient is reduced, inhibited, or suppressed.

Remarks

Applicants' response is timely filed on May 28, 2002 with a 3 month extension of time to the Office Action mailed December 3, 2002.

Applicants acknowledge the election of Group I. As a result, claims 1-13 are pending. Claims 1 and claim 2 are now combined, and claim 2 is cancelled. Claims 1, 3 and 4 have been amended to more narrowly clarify Applicants' invention. No substantive change has been made by amendment, and no new matter has been added to the application.

The Examiner has indicated that the information disclosure statement filed on July 10, 2002 fails to comply with the provisions of 37 CFR 1.97 because the copies of the cited patent and non-patent references were missing from the submission. However, contrary to what was forwarded to the attention of the Examiner, all patent and non-patent references cited in Applicants' Form 1449, and were attached thereto at the time it was initially received by the US Patent and Trademark Office.

As evidence that Applicants filed a complete Information Disclosure Statement and all cited references (A-F and 1-85), mailed on June 8, 2002 and received by the US Patent and Trademark Office on July 10, 2002, Applicants submit herewith a copy of the date stamped

return receipt card which acknowledges receipt on July 10, 2002 by the U.S. Patent Office of an "Information Disclosure Statement w/Forms PTO 1449 (11 sheets), references A-F and 1-85." Applicants also enclose herewith, another copy of the references A-F and 1-85, as originally filed on July 10, 2002.

In view of the foregoing, Applicants respectfully request that all references be considered timely filed and that they be reviewed by the Examiner prior to further examination of this application. Should any reference cited therein be the basis for additional rejection, such rejection should not be final, since the loss of the originally filed references and the lack of their availability to the Examiner was not within Applicants' control.

Response to the rejection under 35 USC §112, first paragraph.

The Examiner has rejected claims 1-13 under 35 USC §112, first paragraph as failing to enable the invention that is as broadly claimed as that which was originally filed. Applicants appreciate the comments made by the Examiner regarding 35 USC §112, first paragraph, in light of which Applicants have combined claims 1 and 2, thereby more narrowly defining the chronic inflammation suffered by the patient with an autoimmune disease for the purposes of the presently claimed invention as a "neuroinflammation" in accordance with the examples and disclosure provided by Applicants' in the application. In addition, although Applicants' have show that such neuroinflammation has been prevented from occurring in autoimmune patients, in the interest of furthering this case to allowance, and because the Examiner has viewed the term "prevent" as an absolute term without variation by degree, Applicants have narrowed the claims so that the method claimed is one of reduction, inhibition, or suppression of the neuro-inflammation without range or limitation.

Consequently, the Examiner's rejection is moot on the issue of whether all chronic inflammatory autoimmune diseases may be treated by the present invention, and as to whether Applicants' description can prove that prevention has been absolutely achieved in every case.

The Examiner has further asked for a definition of the terms used in Figure 10, which is important for showing the effectiveness of Applicants' invention. Accordingly Applicants have amended the language associated with the description of the Figure describing the effect of the treatment on brain and spinal cord. The terms "sc," therefore refer to the effects on the "spinal cord." Specifically, "sc(c)" refers to the cervical region of the spinal cord, "sc(t)" refers to the

thoracic region of the spinal cord, "sc(l) refs to the lumbar region of the spinal cord, and "sc(s)" refers to the sacral region of the spinal cord. The abbreviated terms are self- evident to one of ordinary skill in the art and to one having any familiarity at all with the regions of the spinal cord. However, to make the specification as clear to the public as possible, Applicants have amended the specification to more clearly define the abbreviations.

The asterisk (*) symbol is used in each graph in the preceding figures of Applicants' present application to indicate that there is a statistically significant difference between the results found in the untreated specimens as compared with the BBI/BBIC treated specimens. Thus, the asterisks quite simply mean that the data presented in the graph is statistically and significantly different in the level of demyelination seen in the untreated EAE Lewis rats, as compared with those treated using BBI/BBIC.

In light of the amendment to the description of FIG. 10, the Examiner's concerns regarding the disclosure provided therein is now moot.

The Examiner has further expressed a concern in view of the ability of one of ordinary skill in the art to use Bowman Birk Inhibitor derived from a variety of legumes. The Examiner has asserted that only soybean-derived BBI is taught by Applicants, and that as a result, one of ordinary skill in the art attempting to practice the invention would be concerned about toxicity if other sources of BBI/BBIC were used. In response, Applicants respectfully point out that such concerns are completely unfounded. There is no possibility of toxicity when BBI/BBIC is used in accordance with the methods of the present invention. Such concerns could arise only if a partial statement, such as that which is quoted by the Examiner, were to be taken out of context.

In fact, Applicants repeatedly state, at least at pages 2, 16, 17 and 18 of the specification, that use of BBI is completely safe, and that there are no concerns associated with the use of dietary administration of BBI, regardless of the source. The partial sentence quoted by the Examiner when taken out of context appears to suggest that toxicity is a possibility. In contrast however, the paragraph bridging pages 17 and 18 states that:

> "The only toxicity which has previously been associated with BBI/BBIC treatment of animals has been that of causing toxicity to the developing embryo **when injected at an extremely high level** into pregnant mice (Kennedy, 1993A-C; Kennedy, 1994). At normal dosages, BBI/BBIC **do not** have teratogenic effects; in fact, these agents have been shown to prevent birth abnormalities, as has been reviewed by Kennedy, 1993A-C and

Kennedy, 1994. **No toxicity due to BBIC has been reported in any human trial in which BBIC has been used**." (emphasis added)

Upon careful review of the cited Kennedy references that reported the findings when BBI/BBIC is *injected into pregnant females*, and *at extremely high levels* it becomes clear that because the litters produced by those females were of a lower number than normal, some level of toxicity was assumed. The low litter size was not, however, examined further and may have been an artifact resulting from other variables – and not from the injection of the BBI/BBIC per se. Nevertheless, the composition in that case was injected, whereas in the present invention and in all other uses, BBI/BBIC is administered **orally** or as a nutritional supplement. Even in the extreme condition when the BBI/BBIC was injected at far higher than normal dosage no birth defects were recorded, only a low litter number, and in fact the compositions have been used to prevent birth defects.

Accordingly, it would be safe to say that any concerns about toxicity are vastly overstated. Nevertheless, to continue the quoted paragraph, for the present use of **dietary BBI/BBIC**, early human clinical trials with BBIC are limited to post-menopausal females so that potential problems for a developing embryo can not occur. For safety purposes, toxicity studies accompany the present invention as shown in Tables 1 and 2 – but of course, no toxicity was found. As a result, even on a theoretical basis, the **oral** doses of BBI/BBIC used in the treatment of MS would not create a toxicity problem in human patients.

Therefore, as noted at page 17, although presently available in concentrates extracted from soybeans, "BBI is also found in other members of the legume family of plants, such as adzuki beans, black beans, black-eyed peas, peas, lima beans, kidney beans, navy/white beans, pinto beans, chick peas, peanuts, lentils and the like." Many of the references cited in Applicants' IDS attest to the safe and effective applicability of BBI from other legume sources. BBIC was originally developed as a cancer preventive agent. A number of agents with chymotrypsin inhibitory (CI) activity have the ability to prevent the malignant transformation of cells in culture. The region of BBI containing the CI activity is characterized in Applicants' reference 84, Yavelow *et al.*, *Proc. Natl. Acad. Sci. USA* 82:5395 (1985). The existence of the CI value established uniformity of dosage and effect regardless of the legume source of the BBI. Therefore, as stated on page 17, "Although the resulting concentrates may not have the same CI

values as soybean BBIC, the key factor is that there is some degree of chymotrypsin inhibition. Thus, the resulting concentrate would be quantifiable in CI units."

The CI activity is thought to be closely correlated with anti-inflammatory activity, as active oxygen species are thought to play a major role in inflammation (reviewed by Troll *et al.*). Thus, it is thought that all agents with CI activity will have anti-inflammatory and neuro-inflammatory activity. Toxicity , however, is simply not a valid cause for concern in the present application, regardless of the source of the BBI – just as it has not been a concern in earlier applications that have applied other methods. Thus, the BBI can be extracted for use in Applicants' invention from any and all legumes, provided however, that a BBI can be so extracted that has at least a measurable level of CI activity.

Thus, this concern is also now moot.

Accordingly, all of the objections and rejections under 35 USC §112, first paragraph have been rendered moot, and Applicants respectfully request that the entire rejection be withdrawn.

Response to the rejections under 35 USC §112, second paragraph.

The Examiner has rejected claims 1-4 under 35 USC § 112, second paragraph as failing to clearly claim the subject matter of the invention. In making this rejection, the Examiner has noted a requirement for an antecedent basis in claim 4 and has suggested the necessary amendment to correct the problem. Applicants' appreciate the Examiner's suggestion and have amended claim 4 accordingly. Thus the rejection is moot, and Applicants' respectfully seek withdrawal of the rejection.

Response to the rejections under 35 USC §102.

The Examiner has rejected claims 1 and 6-12 under 35 USC § 102(b) as anticipated, over Kennedy *et al.* (A), with evidence provided by Das (B), Hassig (N) and Okamoto *et al.* (O). In making this rejection, the Examiner states that Kennedy *et al.* (A) teaches a method of treating chronic inflammation in a patient (autoimmune inflammatory bowel diseases, *e.g.*, Crohn's disease or ulcerative colitis) comprising administering BBI/BBIC. However, as noted above, Applicants have narrowed the scope of the claims of the present invention to methods for the treatment of autoimmune neuroinflammatory diseases, none of which are taught or suggested by Dr. Kennedy in the cited patent. The earlier patent makes no reference to neural tissue and offers

no method of treating neuroinflammation. Consequently, Kennedy *et al.* (A) cannot and does not anticipate Applicants' present invention under 35 USC § 102(b). Accordingly, Applicants respectfully request that the rejection be withdrawn.

Response to the rejection under 35 USC §103.

The Examiner has rejected claims 1 and 6-13 under 35 USC § 103 as obvious over Kennedy *et al.* (A), with evidence provided by Das (B), Hassig (N) and Okamoto *et al.* (O) for the above-stated reasons. In making this rejection, the Examiner states that it would be obvious to one of ordinary skill in the art to modify the method taught by Dr. Kennedy in reference A to add additional drugs, medicaments, etc to achieve the desired results disclosed in the present invention. If that were true – and Applicants do not believe that to be the case – one would still only add the additional drugs, medicaments etc. to achieve treatment of autoimmune inflammation as related to the bowel of the patient.

However, as noted above, Applicants have narrowed the scope of the claims of the present invention to methods for the treatment of autoimmune neuroinflammatory diseases, none of which are taught or suggested by Dr. Kennedy in the cited patent. The earlier patent makes no reference to neural tissue and offers no method of treating neuroinflammation. Consequently, Kennedy *et al.* (A) cannot and does not anticipate Applicants' present invention under 35 USC § 103. Accordingly, Applicants respectfully request that the rejection under § 103 be withdrawn.

Response to the double patenting rejection.

The Examiner has made a nonstatutory double patenting rejection of claims 1 and 12 , and also of claims 1 and 6-11, as being unpatentable over claims 1 and 2 of US Patent 5,614,198. However, contrary to the Examiner's comments, and as described in detail above, none of the cited references, including US Patent 5,614,198, discloses or even suggests the method of treating a treating chronic neuroinflammation in a patient with neuroinflammatory autoimmune disease comprising administering to the patient an amount of Bowman Birk Inhibitor effective to reduce, inhibit, or suppress the chronic inflammation. In the cited patent, Dr. Kennedy makes no reference to neural tissue and offers no method of treating neuroinflammation. Consequently, the present invention is in no way anticipated by, or an obvious variation of, the earlier patent of

Kennedy *et al.*, and no terminal disclaimer is necessary to prevent one or more of the Applicants from extending their right of exclusivity in a subsequent patent.

All pending claims depend on claim 1. As a result, once claim 1 has been distinguished from the cited US patent, all claims dependent thereon are also distinguished, even though they may restate certain elements, albeit on a different and patentably distinct base-claim.

Accordingly Applicants again point to the substantial (and patentable) differences between the prior art configurations and that of the present invention. The present invention quite simply operates in a completely different manner from the prior art, and produces a treatment of chronic inflammation in neural tissue, which is very different from chronic inflammation in soft tissues, such as the bowel. Thus, the prior art fails to anticipate Applicants' invention or render it obvious, and Applicants respectfully request that in light of the foregoing, the rejection under the double patenting rejection be reconsidered and withdrawn.

In sum, Applicants assert that all pending claims are in condition for allowance, and respectfully request that allowance be granted at the earliest date possible. Should the Examiner have any questions or comments regarding Applicants' amendments or response, she is asked to contact Applicants' undersigned representative at (215) 575-7034.

Respectfully submitted

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Version with markings to show changes made

In the Specification:

At page 3, the paragraph beginning at line 1, has been changed as shown:

Absorbed BBI is measurable using antibodies to reduced BBI, produced by injection into experimental animals and utilized in immunoassays (Wan *et al.*, 1995). BBI has been assessed in the blood, tissue and urine of rodents and dogs after the ingestion of BBIC permitting pharmacokinetic studies, although it has not yet been feasible to measure BBI levels in the blood of humans after oral BBIC dosing. However, it has been found in the urine, starting within several hours after a single oral dose (Wan *et al.*, *Cancer Epidem. Biomarkers & Prevention* [~~9:741-747 (2000)~~] 8:601-608 (1999)). Of note, studies in orally-dosed animals have shown that some BBI can be subsequently found in the CNS even when the blood-brain barrier is intact (Kennedy, AR, personal communication).

At page 4, the paragraph beginning at line 9, has been changed as shown:

It is also known that BBI, as well as several other inhibitors of chymotrypsin proteolytic activity, have the ability to prevent the induction of superoxide anion radicals and hydrogen peroxide from stimulated human polymorphonuclear leukocytes and macrophage-like cells (Frenkel *et al.*, *Carcinogenesis* 8:1207-1212 (1987); Ware *et al.*, [~~*Cancer and Nutrition*~~] *Nutr. Canc.* 33:174-177 (1999)). Proteases and free radicals produced by macrophages are closely associated with the production of inflammation. For example, Multiple Sclerosis (MS) is characterized by inflammation and increased numbers of activated immunocytes of macrophage and T cell lineage (Hauser *et al.*, In Harrison's Principles of Internal Medicine. Fauci *et al.* (eds). New York, McGraw-Hill, 1998, pp. 2409-2419).

At page 5, the paragraph beginning at line 5, has been changed as shown:

Proteases are associated with many facets of immune system function and immune system disorders (Cuzner *et al.*, *J. Neuroimmunol.* [~~94~~] 6:1-14 (1999); Vaday *et al.*, *J. Leukoc. Biol.* 67:149-159 (2000)). A variety of proteases are increased in MS lesions, including lysosomal proteases and matrix metalloproteinases gelatinase A and B (MMP-2 and 9, respectively) (Cuzner *et al.*, 1999; Halonen *et al.*, *J. Neurol. Sci.* 79:267-274 (1987); Kieseier *et al.*, *Curr. Opin. Neurol.* 12:323-336 (1999); Hartung *et al.*, *J. Neuroimmunol.* 107:140-147

(2000); Bever *et al.*, *Neurology* 53:1380-1381 (1999); Maeda *et al.*, *J. Neuropathol. Experimental Neurol.* 55:300-309 (1996)).

At page 11, the paragraph beginning at line 24, has been changed as shown:

FIG. 10 graphically depicts the effect of BBIC for the treatment of Lewis rats with EAE, showing the difference in inflammatory demyelination in the CNS (brain and spinal cord) of BBIC-treated animals as compared with matching, untreated control animals. In the bar graph the first column provides data on the effect in "brain" tissue, while the remaining 4 columns provide data from various regions of the spinal cord ("sc"). Specifically, "sc(c)" refers to the cervical region of the spinal cord, "sc(t)" refers to the thoracic region of the spinal cord, "sc(l) refers to the lumbar region of the spinal cord, and "sc(s)" refers to the sacral region of the spinal cord. The asterisks (*) are used as noted above to show that there is a statistically significant change between the data from the untreated animals and the data from the matched treated animals.

In the claims:

Claims 1, 3 and 4 have been amended as follows:

1. (Amended) A method for treating chronic [~~inflammation~~] neuroinflammation in a patient with [~~inflammatory~~] neuroinflammatory autoimmune disease comprising administering to the patient an amount of Bowman Birk Inhibitor effective to reduce, inhibit, or suppress [~~or prevent~~]the chronic inflammation.
3. (Amended) The method of claim [~~2~~] 1, wherein the neuroinflammation affects the central nervous system or peripheral nervous system of the patient.
4. (Amended) The method of claim 3, wherein demyelination of the [~~nerve~~] neural tissue of the patient is reduced, inhibited, or suppressed [~~or prevented~~].